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The EMT-activator ZEB1 promotes tumorigenicity by repressing stemness-inhibiting microRNAs.

Wellner U, Schubert J, Burk UC, Schmalhofer O, Zhu F, Sonntag A, Waldvogel B, Vannier C, Darling D, zur Hausen A, Brunton VG, Morton J, Sansom O, Schüler J, Stemmler MP, Herzberger C, Hopt U, Keck T, Brabletz S, Brabletz T.

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Invasion and metastasis of carcinomas is promoted by the activation of the embryonic 'epithelial to mesenchymal transition' (EMT) program, which triggers cellular mobility and subsequent dissemination of tumour cells. We recently showed that the EMT-activator ZEB1 (zinc finger E-box binding homeobox 1) is a crucial promoter of metastasis and demonstrated that ZEB1 inhibits expression of the microRNA-200 (miR-200) family, whose members are strong inducers of epithelial differentiation. Here, we report that ZEB1 not only promotes tumour cell dissemination, but is also necessary for the tumour-initiating capacity of pancreatic and colorectal cancer cells. We show that ZEB1 represses expression of stemness-inhibiting miR-203 and that candidate targets of miR-200 family members are also stem cell factors, such as Sox2 and Klf4. Moreover, miR-200c, miR-203 and miR-183 cooperate to suppress expression of stem cell factors in cancer cells and mouse embryonic stem (ES) cells, as demonstrated for the polycomb repressor Bmi1. We propose that ZEB1 links EMT-activation and stemness-maintenance by suppressing stemness-inhibiting microRNAs (miRNAs) and thereby is a promoter of mobile, migrating cancer stem cells. Thus, targeting the ZEB1-miR-200 feedback loop might form the basis of a promising treatment for fatal tumours, such as pancreatic cancer.

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